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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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BESPAK PLC [/]; (). BARNES, Paul [/]; (). LECHNER, Marc [/]; (). WARBY, Richard, John [/]; (). BARNES, Paul [/]; (). LECHNER, Marc [/]; (). WARBY, Richard, John [/]; (). BOULT WADE TENNANT ; ().

Published

(54) **Title: IMPROVEMENTS IN DRUG DELIVERY DEVICES**
(54) **Titre: PERFECTIONNEMENTS APPORTES A DES DISPOSITIFS D'ADMINISTRATION DE MEDICAMENTS**

(57) Abstract

The invention relates to improvements to drugs delivery devices, in particular, those for dispensing a metered dose of medicament. There is provided apparatus (10, 110) for dispensing a medicament wherein at least a portion of one or more of the surfaces of components of the apparatus which come into contact with the medicament during storage or dispensing has a layer of a poly-para-xylylene polymer also known as parylene bonded to at least a portion thereof.

(57) Abrégé

L'invention concerne des perfectionnements apportés à des dispositifs d'administration de médicaments, en particulier, à des dispositifs d'administration d'une quantité dosée d'un médicament. L'invention concerne en conséquence un appareil d'administration d'un médicament (10, 110), caractérisé en ce qu'au moins une partie d'une ou de plusieurs des surfaces des composants de l'appareil venant en contact avec le médicament durant l'entreposage ou l'administration présente une couche d'un polymère poly-para-xylylène, également connu sous la désignation de _ parylène _, liée à au moins une partie de la surface.

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(71) Applicant (*for all designated States except US*): BESPAK PLC [GB/GB]; Bergen Way, North Lynn Industrial Estate, King's Lynn, Norfolk PE30 2JJ (GB).

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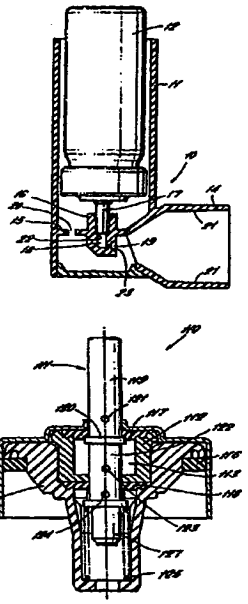
Without international search report and to be republished upon receipt of that report.

(54) Title: IMPROVEMENTS IN DRUG DELIVERY DEVICES

(57) Abstract

The invention relates to improvements to drugs delivery devices, in particular, those for dispensing a metered dose of medicament. There is provided apparatus (10, 110) for dispensing a medicament wherein at least a portion of one or more of the surfaces of components of the apparatus which come into contact with the medicament during storage or dispensing has a layer of a poly–para–xylylene polymer also known as parylene bonded to at least a portion thereof.



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Description

IMPROVEMENTS IN DRUG DELIVERY DEVICES

This invention relates to improvements in drug delivery devices and particularly those for dispensing a metered dose of a medicament.

In metered dose inhalers, an aerosol stream from a pressurised dispensing container is fired towards a patient or user of the inhaler into an air flow. The air flow is created by a user inhaling through a mouthpiece of the inhaler and the medicament is released into this air flow at a point between the air inlet holes and the mouthpiece.

Conventional metering valves for use with pressurised dispensing containers comprise a valve stem coaxially slidable within a valve member defining an annular metering chamber, and outer and inner annular seals operative between the respective outer and inner ends of the valve stem and the valve member to seal the metering chamber therebetween. The valve stem is hollow whereby in a non-dispensing position of the valve stem, the metering chamber is connected to the container and charged with product therefrom. The valve stem is movable against the action of a spring to a dispensing position wherein the metering chamber is isolated from the container and vented to atmosphere for the discharge of product.

Other drug delivery devices include apparatus in which capsules containing a powdered medicament are mechanically opened at a dispensing station where inhaled air subsequently entrains the powder, which is then dispensed through a mouthpiece.

A problem with all such drug delivery devices is that deposition of the medicament, or a solid component from a suspension of a particulate product in a liquid propellant, on the internal surfaces and

other components of the devices occurs after a number of operation cycles and/or storage. This can lead to reduced efficiency of operation of the device and of the resulting treatment in that deposition of the product reduces the amount of active drug available to be dispensed.

Some prior art devices rely on the dispenser being shaken in an attempt to dislodge the deposited particles as a result of the movement of a liquid propellant and product mixture. However, whilst this remedy is effective within the body of the container itself, it is not effective for particles deposited on the inner surfaces of the metering chamber. As the size of the chamber is significantly smaller, the restricted flow of fluid in the metering chamber (caused by the tortuosity of the flow path through the chamber) means that the fluid in the metering chamber does not move with enough energy to adequately remove the deposited particles.

One solution is proposed in our pending application GB 9721684.0 in which a liner of a material such as fluoropolymer, ceramic or glass is included to line a portion of the wall of a metering chamber in a metering valve. Although this solves the problem of deposition in these types of dispensers, it does require the re-design or modification of mouldings and mould tools for producing the valve members to allow for the insertion of the liner.

It is an object of the present invention to provide drug delivery devices in general in which the deposition of the product and active drug component is minimised.

According to the invention there is provided apparatus for dispensing a medicament wherein at least a portion of one or more of the surfaces of components

of the apparatus which come into contact with medicament during storage or dispensing has a layer of a poly-para-xylylene polymer also known as Parylene bonded to at least a portion thereof.

A particular embodiment of the present invention will now be described, by way of example only, with reference to the accompanying drawings in which;

Fig. 1 is a cross-sectional view through an inhaler, which is one type of drug delivery device of the present invention; and

Fig. 2 is a cross sectional view of a metering valve used in another type of drug delivery device.

In Fig. 1 an inhaler 10 for a product such as a medicament comprises a housing 11 for receiving a pressurised dispensing container 12 of a medicament and a mouthpiece 14 for insertion into the mouth of a user of the inhaler 10.

The container housing 11 is generally cylindrical and open at its upper end. A lower wall 15 of the housing 11 includes an annular socket 16 for receiving the tubular valve stem 17 of the container 12. The socket 16 communicates via a duct 18 ending in an orifice 19 with the mouthpiece 14. The lower wall 15 also has holes 20 for allowing air to flow through the container housing 11 into the mouthpiece 14.

The mouthpiece 14 may be generally circular or shaped to fit the mouth and is connected to or forms a part of the housing 11.

In use, a patient or user holds the inhaler 10, usually in one hand, and applies his mouth to the mouthpiece 14. The user then inhales through the mouthpiece 14 and this creates an airflow through the

cylindrical housing 11, from its open end around the dispensing container 12, through the holes 20 and into the mouthpiece 14. After the user has started inhaling through the mouthpiece 14, the container 12 is depressed downwardly onto its stem 17 to release a dose of medicament from the container 12. The dose of medicament is projected by the pressure in the container 12 via the duct 18 and through the orifice 19. It then mixes with the airflow through the mouthpiece 14 and is hence inhaled by the user.

In traditional inhalers, all of the components are plastic mouldings, which gives rise to the deposition problems described above. The particular problem areas in devices such as inhalers are the internal surfaces 21 of the mouthpiece 14, the internal surfaces 22 of the duct 18 and the walls 23 defining the orifice 19. In some inhalers 10, the diameter of at least a part of the duct 18 can be as little as 0.5mm and so any deposition on its internal surfaces 22 could lead to not only the problem of a reduction in active drug components being available, but also dispensing difficulties.

The metering valve 110 illustrated in Fig. 2 is another type of drug delivery device or dispenser, and includes a valve stem 111 which protrudes from and is axially slidable within a valve member 112, the valve member 112 and valve stem 111 defining therebetween an annular metering chamber 113. The valve member 112 is located within a valve body 114 which is positioned in a pressurised container (not shown) containing a product to be dispensed. The metering valve 110 is held in position with respect to the container by means of a ferrule 115 crimped to the top of the container and sealing being provided between the valve body 114 and container by an annular gasket 116.

An outer seal 117 and an inner seal 118 of an elastomeric material extend radially between the valve stem 111 and the valve member 112. The outer seal 117 is radially compressed between the valve member 112 and valve stem 111 so as to provide positive sealing contact, the compression being achieved by using a seal which provides an interference fit on the valve stem 111 and/or by the crimping of the ferrule 115 onto the pressurised container during assembly.

The valve stem 111 has an end 119 which protrudes from the valve member 112 and ferrule 115 which is a hollow tube and which is closed off by flange 120 which is located within the metering chamber 113. The hollow end 119 of valve stem 111 includes a discharge port 121 extending radially through the side wall of the valve stem 111. The valve stem 111 further has an intermediate section 122, which is also hollow and defining a central passage and which has a pair of spaced radial ports 123, 124 which are interconnected through a central cavity.

A spring 125 extends between a second flange 126, separating the intermediate section 122 of the valve stem 111 and an inner end 127 of the valve stem 111, and an end of the valve body 114 to bias the valve stem 111 in a non-dispensing position in which the first flange 120 is held in sealing contact with the outer seal 117. The second flange 126 is located outside the valve member 112, but within the valve body 114.

The metering chamber 113 is sealed from the atmosphere by the outer seal 117, and from the pressurised container to which the valve 110 is attached by the inner seal 118. In the illustration of the valve 110 shown in Fig. 2 radial ports 123, 124 together with the central cavity in the intermediate

section 122 of the valve member 111 connect the metering chamber 113 with the container so that in this non-dispensing condition the metering member 113 will be charged with product to be dispensed.

Upon depression of the valve stem 111 relative to the valve member 112 so that it moves inwardly into the container, the radial port 124 is closed off as it passes through the inner seal 118, thereby isolating the metering chamber 113 from the contents of the pressurised container. Upon further movement of the valve stem 111 in the same direction to a dispensing position the discharge port 121 passes through the outer seal 117 into communication with the metering chamber 113. In this dispensing position the product in the metering chamber 113 is free to be discharged to the atmosphere via the discharge port 121 and the cavity in the hollow end 119 of the valve stem 111.

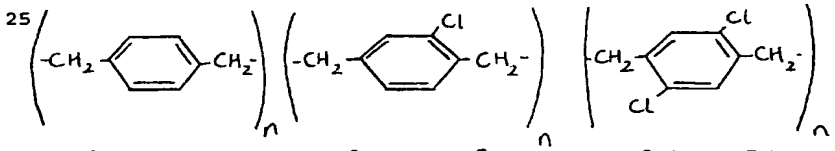
When the valve stem 111 is released, the biasing of the return spring 125 causes the valve stem 111 to return to its original position. As a result the metering chamber 113 becomes recharged in readiness for further dispensing operations.

The component parts of conventional drug dispensing devices, such as valve members, valve stems, inhaler housings and so on, are generally formed as single mouldings from material such as acetal, polyester or nylon which are prone to the deposition problems described above. Although in some cases it might be possible to include a separate liner of a material such as a fluoropolymer, ceramic or glass to line a portion of the area in which deposition problems occurs, this requires the re-design or modification of mouldings and mould tools so that the components can accommodate such lines.

In the present invention we propose a solution in

which the component parts of the drug dispensing devices are made by conventional tooling and moulds from the traditional materials listed above. They are then coated with a thin layer of a polymer from the poly-para-xylylene family, also known as the Parylene family, preferably using a Vapour Deposition Polymerisation (VDP) technique. Whilst the poly-para-xylylene polymer may be applied by spray coating or dipping, VDP has the advantage that the poly-para-xylylene coating is formed spontaneously on the component parts at or near room temperatures. Thus thermoplastic materials such as polybutyrene terephthalate (PBT), nylon, acetal and tetrabutyrene terephthalate (TBT) can be treated without fear of thermal damage.

It has been found that coating the surface of component parts with Parylene significantly reduces the deposition of active drugs on the relevant surfaces due to factors such as high conformity, absence of pinholes and coefficients of static and dynamic friction between 0.25 and 0.35 giving good friction reduction. Parylene exists in three variants, commonly referred to as Parylene N, Parylene C and Parylene D, as shown below.



PARYLENE N PARYLENE C PARYLENE D

Parylene N has been found to exhibit the best anti-frictional properties (coefficient of static friction 0.25, coefficient of dynamic friction 0.25) and is thus preferred in use over Parylene C and D

where low friction is important.

Either an entire component within the drug delivery device, or just the surfaces of one or more component which would come into contact with the medicament during actuation, could be treated to provide an improved drug delivery device according to the present invention. In the case of the type of inhalers as shown in Fig. 1, surfaces 21, 22 and 23 may be treated. In a typical dry powder inhaler, the inner surface of the mouthpiece and any channel leading to the mouthpiece from the point of powder storage, i.e. from a capsule, bulk storage chamber or a pre-metered chamber of a device. In the metering valve of Figure 2, the valve member 112 alone may be treated. However additional benefits can be achieved in treating some or all of the other plastic and rubber parts of the valve, including, for example, the valve body 114 and the seals 116, 117 and 118. In addition, the metal parts exposed to the drug formulation may also be treated, for example, the ddispensing container 12, the spring 125 or the ferrule 115. The method can also be used to treat components of many other delivery devices including nasal pumps, non-pressurised actuators, foil storage types, breath actuated inhaler devices and breath co-ordinating devices and so on.

Claims

CLAIMS:

1. Apparatus for dispensing a medicament wherein at least a portion of one or more of the surfaces of components of the apparatus which come into contact with medicament during storage or dispensing has a layer of a poly-para-xylylene polymer also known as Parylyne bonded to at least a portion thereof.

2. Apparatus as claimed in claim 1 in which the polymer is one of Parylene C, Parylene N or Parylene D.

3. Apparatus as claimed in claim 1 or claim 2 in which the treated portion is made from a plastic polymer or synthetic rubber.

4. Apparatus as claimed in claim 1 or claim 2 in which the treated portion is made from a metal or alloy.

5. Apparatus as claimed in any one of the preceding claims in which the apparatus comprises a housing adapted to receive a container for storing the medicament, a mouthpiece and duct means connecting an outlet of the container with the mouthpiece, and at least a portion of one or more of the internal surfaces of the duct and/or mouthpiece is treated.

6. Apparatus as claimed in claim 5 in which at least a portion of the surfaces of the duct and the mouthpiece have a layer of poly-para-xylylene polymer bonded thereto.

7. Apparatus as claimed in any one of claims 1 to 4

in which the apparatus is a metering valve for use with a pressurised dispensing container, the valve comprising a valve stem co-axially slidable within a valve member, said valve member and valve stem defining an annular metering chamber, outer and inner annular seals operative between the respective outer and inner ends of the valve member and the valve stem to seal the annular metering chamber therebetween, wherein at least a portion of the metering valve is treated to have a layer of a poly-para-xylylene polymer bonded to at least a portion of an internal surface of the metering chamber.

8. Apparatus as claimed in claim 7 in which at least a portion of the surface of the valve member has the layer of poly-para-xylylene polymer bonded thereto.

9. Apparatus as claimed in claim 7 or claim 8 in which at least a portion of the surface of the valve stem or inner end has the layer of poly-para-xylylene polymer bonded thereto.

10. Apparatus as claimed in any one of claims 7 to 9 in which at least a portion of the surface of the seals have the layer of poly-para-xylylene polymer bonded thereto.

11. Apparatus as claimed in any one of claims 7 to 10 in which the valve further comprises a valve body in which the valve member is located, the valve body having the layer of poly-para-xylylene polymer bonded to at least a portion of its surface.

12. Apparatus as claimed in any one of claims 7 to 11 further comprising a gasket extending between the

sealing surfaces of the metering valve and a pressurised dispensing container, said gasket having the layer of poly-para-xylylene polymer bonded to at least a portion of the surface thereof.

13. Apparatus as claimed in any preceding claim wherein the internal surfaces of components are coated with the poly-para-xylylene polymer by vapour deposition polymerisation.

14. Apparatus substantially as hereinbefore described with reference to and as shown in the accompanying drawings.

FIG. 1.

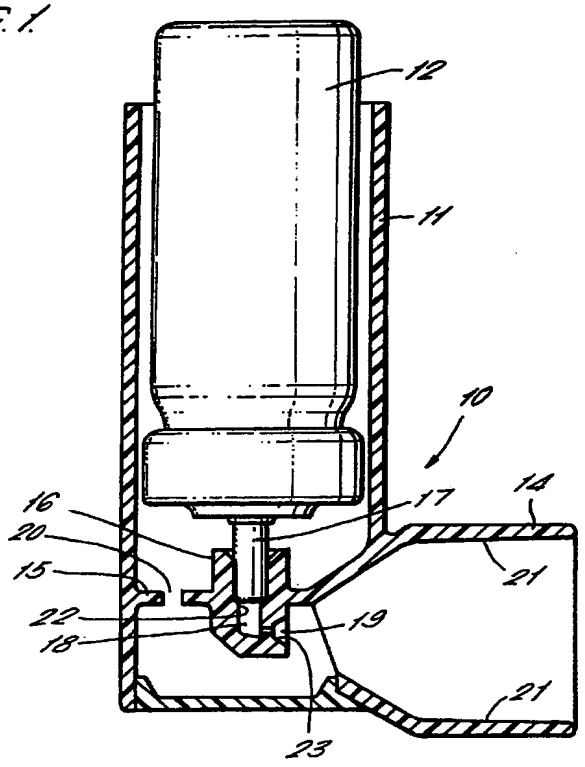
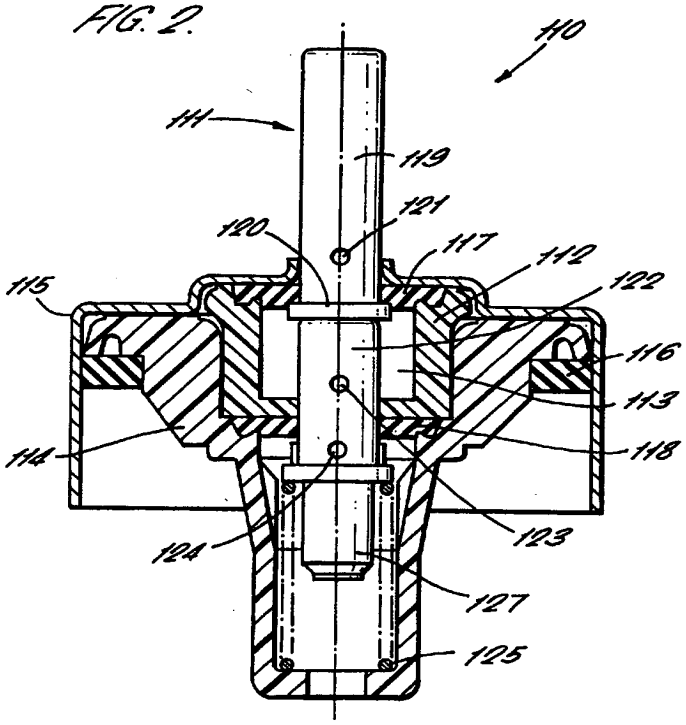


FIG. 2.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CLAIMS

By coating endovascular protheses with amphiphylic polyurethanes, we have developed an efficient method to treat blood vessel stenosis. This method proved to considerably limit the thrombogenicity as well as the rejection against endovascular protheses so that this method signifies an important step forward in the treatment of blood vessel stenosis.

INTERNATIONAL SEARCH REPORT

Inten ial Application No
PCT/BE 94/00024

A. CLASSIFICATION OF SUBJECT MATTER
IPC 5 A61L31/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 5 A61L

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP,A,0 518 704 (SCIMED LIFE SYSTEMS) 16 December 1992 see claims 3,4,9-13	1
Y	WO,A,87 04935 (FISCHEL R.E.) 27 August 1987 see claim 11	1
Y	WO,A,92 15286 (NOVA PHARMACEUTICAL) 17 September 1992 see page 1, line 9 - line 21; claims 1,2,5; example 5	1
P,A	EP,A,0 566 245 (MEDTRONIC) 20 October 1993 see claims 1,3,5,28	1

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

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"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
1 June 1994	08. 06. 94

Name and mailing address of the ISA	Authorized officer
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Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Inter: ıal Application No
PCT/BE 94/00024

C.(Conunuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US,A,4 371 686 (YAMAMOTO N.) 1 February 1983 see column 1, line 6 - line 22	1

2

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

rnational application No.
PCT/BE 94/00024

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
"Remark: Although claim 1 is directed to a method of treatment of the human/animal body the search has been carried ot and based on the alleged effects of the product."

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

...formation on patent family members

Inter ...al Application No
PCT/BE 94/00024

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
EP-A-0518704	16-12-92	JP-A-	5200048	10-08-93
WO-A-8704935	27-08-87	DE-A-	3786721	02-09-93
		EP-A,B	0257091	02-03-88
		EP-A-	0556940	25-08-93
		US-A-	4768507	06-09-88
WO-A-9215286	17-09-92	AU-A-	1579092	06-10-92
EP-A-0566245	20-10-93	JP-A-	6007455	18-01-94
US-A-4371686	01-02-83	JP-C-	1184116	27-12-83
		JP-A-	57051718	26-03-82
		JP-B-	58008700	17-02-83